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Early neurophysiological stimulus processing during a performance-monitoring task differentiates women with bipolar disorder from women with ADHD

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ABSTRACT

Adults with attention-deficit/hyperactivity disorder (ADHD) or bipolar disorder (BD) may display similar cognitive impairments and clinical symptoms, which might reflect shared mechanisms. Initial evidence indicates disorder-specific and overlapping neurophysiological alterations using event-related potentials (ERPs) in individuals with BD or ADHD during attentional tasks, but it is unknown whether impairments generalize across other processes and tasks. We conduct the first comparison between women with ADHD ($n = 20$), women with BD ($n = 20$) and control women ($n = 20$) on ERPs from a performance-monitoring flanker task. The BD group showed a significantly attenuated frontal ERP of conflict monitoring (N2) compared to the ADHD group across both low-conflict (congruent) and high-conflict (incongruent) task conditions, and compared to controls in the high-conflict condition. However, when controlling for an earlier attentional ERP (frontal N1), which was significantly reduced in participants with BD compared to participants with ADHD and controls, N2 group differences were no longer significant. These results indicate that ERP differences in conflict monitoring may be attributable to differences in earlier attentional processes. These findings identify neural differences in early attention between BD and ADHD which precede conflict monitoring processes, potentially pointing to distinct neural mechanisms implicated in the two disorders.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) and bipolar disorder (BD) are distinct psychiatric diagnoses (APA, 2013) sharing several impairing symptoms, such as increased impulsivity, distractibility and talkativeness (Asherson et al., 2014; Franke et al., 2018; Kitsune et al., 2016; Skirrow et al., 2012). Individuals with ADHD or BD can further display similar cognitive impairments, for example in attention and

response inhibition (Cotrena et al., 2020; Hervey et al., 2004; Vainieri et al., 2020), which may suggest some degree of similarity in the neurobiological processes underlying the two disorders. Importantly, although BD often occurs in distinct episodes (unlike ADHD, which is more chronic), individuals with BD between episodes have been reported to show residual cognitive impairments, such as in distractibility and planning (Samalin et al., 2016, 2014; Torres et al., 2007), that overlap with those seen among individuals with ADHD. Direct

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comparisons between ADHD and BD can provide an improved understanding of the differences and commonalities in the neurocognitive processes underlying the two disorders.

Since similar cognitive and clinical profiles may arise from different neurobiological pathways (Banaschewski and Brandeis, 2007), the investigation of brain activity with event-related potentials (ERPs) in cross-disorder studies may advance our understanding of the distinct and shared impairments associated with ADHD and BD. ERPs allow the examination of changes in brain activity in response to certain events, such as task stimuli, with millisecond temporal resolution (Banaschewski and Brandeis, 2007). The very few direct cross-disorder ERP comparisons carried out to date have found both disorder-specific and overlapping impairments in ERP components. One study found that the amplitude of a P3 component occurring around 300–500 ms after the presentation of rewarding stimuli (an index of reward sensitivity) during a gambling task was reduced in 12 adults with ADHD and in 13 adults with BD compared to 25 controls (Ibanez et al., 2012). This study also found that this P3 measure was not modulated by increasing rewards in the ADHD group, unlike the other groups, suggesting that those with ADHD may be less sensitive to changes in reward magnitude. More recently, we found shared reductions in the amplitude of a P3 in response to non-target stimuli, reflecting impaired response inhibition, during a Cued Continuous Performance Task (CPT-OX) in 20 women with ADHD and 20 with BD compared to 20 control women (Michelini et al., 2016b). In another study in the same sample, we also reported reductions in the contingent negative variation (CNV), a late potential indexing response preparation which is typically observed before the occurrence of the next stimulus, during a four-choice reaction time task (Michelini et al., 2018). Conversely, an N2 component observed 200–400 ms in response to non-target stimuli during the CPT-OX task, reflecting conflict monitoring (i.e., the ability to detect conflict and adjust response selection during goal-directed behaviour; Holroyd et al., 2003; Yeung and Cohen, 2006), was attenuated only in women with BD (Michelini et al., 2016b). This finding therefore suggests a conflict-monitoring impairment that may be specific to BD in women.

Considering these findings further, the intact N2 in the ADHD group aligns with previous studies using the CPT-OX (Albrecht et al., 2013; McLoughlin et al., 2010). Yet, N2 reductions have been reported in studies using variants of the flanker task (Albrecht et al., 2008; McLoughlin et al., 2009; Michelini et al., 2016a), which is specifically designed to probe conflict monitoring in the presence of conflicting stimuli (Eriksen and Schultz, 1979; Kopp et al., 1996; Yeung and Nieuwenhuis, 2009). The N2 reduction observed in the BD group in our previous study (Michelini et al., 2016b) is consistent with two previous studies using an oddball task (Ethridge et al., 2015, 2012), but not with another study indicating no N2 attenuation in a BD sample during a flanker task (Morsel et al., 2014). One possible explanation for the mixed N2 findings across tasks in ADHD and BD samples is that most studies to date have investigated N2 components in isolation, rather than examining if earlier ERPs of more automatic processes have downstream effects on the later N2. Research focused on early ERPs occurring in the first 200 ms after stimulus onset points to early alterations in sensory and pre-attentional ERPs in individuals with BD and psychosis (Butler et al., 2007; Cabranes et al., 2013; Jahshan et al., 2012; Yeap et al., 2009). One of these ERPs is the N1, a negative peak occurring around 100–200 ms which precedes the N2 and reflects early-attentional processes (Dong and Zhong, 2017; Johnstone et al., 2009; Vogel and Luck, 2000). Instead, most previous studies report intact N1 amplitude in individuals with ADHD (Fisher et al., 2011; Johnstone et al., 2009; Woltering et al., 2013). A direct comparison between ADHD and BD groups examining potential differences in earlier stimulus processing may help clarify to what extent ADHD and BD differ on N2 indices of conflict monitoring.

Several studies on the N2 during flanker tasks with participants with ADHD have also examined impairments in closely-related ERP indices of error-processing, the error-related negativity (ERN) and positivity (Pe)

(Albrecht et al., 2008; McLoughlin et al., 2009; Michelini et al., 2016a), to provide a more complete assessment of processes that are jointly referred to as performance monitoring (Yeung and Cohen, 2006). In contrast, only one study to date has examined N2, ERN and Pe in the same BD sample (Morsel et al., 2014). The ERN is an early, automatic neural response observed around 0–150 ms after a mistake (Falkenstein et al., 2001), while the Pe is a subsequent response, occurring around 150–450 ms, thought to represent conscious error processing aimed at optimizing response strategy (Endrass et al., 2007). In ADHD samples, a meta-analysis of 7 studies found reductions in the ERN, but not in the Pe, in individuals with ADHD (Geburek et al., 2013). A more recent review, however, identified almost as many studies that found ERN reductions among individuals with ADHD as those that did not (Meyer and Hajcak, 2019). Reduced Pe was reported in a more recent and larger ADHD sample (Michelini et al., 2016a), but not several other studies of adults with ADHD (Chang et al., 2009; McLoughlin et al., 2009). Mixed evidence on error-related ERPs has also emerged in adults with BD, as the ERN was reduced in two studies (Minzenberg et al., 2014; Morsel et al., 2014) but not in another study (Kopf et al., 2015), while the Pe was intact in the former two studies, but reduced in the latter. No study to date has directly compared individuals with ADHD or BD on these error-processing ERP components.

The present study aimed to directly compare women with ADHD and women with BD on ERP components of performance monitoring (N2, ERN and Pe) during a flanker task. We used an all-female sample (Kitsune et al., 2016; Michelini et al., 2016b, 2018; Rommel et al., 2016), to match the groups on sex and because little is known on these processes in females, especially with ADHD (Albrecht et al., 2008; McLoughlin et al., 2009). Based on previous literature, we hypothesised that the N2 would be reduced in both ADHD and BD groups compared to controls. We further hypothesized that early alterations in the N1 preceding the N2 would be specific to the BD group, congruent with previous studies of individuals with BD (Cabranes et al., 2013; Jahshan et al., 2012; Yeap et al., 2009). Finally, we did not make explicit predictions for the ERN and Pe due to inconsistent findings to date.

2. Methods

2.1. Sample

The sample consisted of 20 women with ADHD, 20 with BD and 20 control women, aged between 20 and 52 years (Table 1). Full information on recruitment, clinical assessment and clinical profiles of this sample can be found elsewhere (Kitsune et al., 2016) and in the Supplementary material (Table S1). Briefly, participants with ADHD were recruited from an adult ADHD clinic, participants with BD from a psychosis clinic and a sample that had previously participated in another study (Hosang et al., 2012), and controls from a volunteer database. Exclusion criteria for all groups were drug or alcohol dependency in the previous 6 months, autism, epilepsy, neurological disorders, brain injury, past ECT treatment, current involvement in another research trial likely to alter symptom severity, pregnancy or a limited proficiency in English language. Individuals with comorbid ADHD and BD were also excluded. Individuals with BD who were experiencing a manic episode

Table 1
Sample demographics (age and IQ) reported by group with group comparisons.

	ADHD Mean (SD)	BD Mean (SD)	Controls Mean (SD)	F	p
Age (years)	39.4 (7.7)	40.3 (7.7)	36.7 (4.3)	1.63	0.21
IQ	104 (17.9)	108 (12.5)	112 (14.2)	1.37	0.26

Group differences on age and IQ score were tested with univariate ANOVAs. ADHD, attention-deficit/hyperactivity disorder; BD, bipolar disorder; F, ANOVA statistic; IQ, intelligence quotient; p, value of significance; SD, standard deviation.

at the time of the assessment were excluded. Control participants with a history of psychiatric disorders or who were taking psychiatric medication were excluded.

Participants in the ADHD group had a current combined-type diagnosis or an inattentive-type diagnosis with sufficient hyperactivity-impulsivity symptoms in childhood to meet a childhood combined-type diagnosis, reflecting the typical adult ADHD clinical population (Asherson et al., 2014). Participants in the BD group had a diagnosis of BD Type-I, having experienced at least one manic episode in the past, but were showing euthymic (i.e. normal) mood at the time of the assessments. IQ and age did not differ between groups (Table 1).

2.2. Procedure

All participants were asked to refrain from caffeinated drinks and nicotine 2 h before assessments. Participants with ADHD who were taking stimulant medication were asked to stop them 48 h prior to the assessment. For ethical reasons, participants were not asked to stop taking mood stabilizers, anti-psychotic medication or anti-depressants they had been prescribed. Full information regarding medication taken by study participants is provided in the Supplementary Material. The study was carried out in accordance with the Declaration of Helsinki (2008). Ethical approval was granted by the Camberwell St Giles Research Ethics Committee (approval number 11/LO/0438) and all participants provided informed written consent after the nature of the procedures had been fully explained.

2.3. Flanker task

The task was an adaption of the Eriksen Flanker paradigm (Eriksen and Schultz, 1979) designed to induce conflict, which was used in previous ERP studies of ADHD (Albrecht et al., 2008; McLoughlin et al., 2009; Michelini et al., 2016a). In each trial a target arrow (black 18 mm equilateral triangle) replaced a central fixation mark. Participants used their left or right index fingers to press corresponding response buttons to indicate the direction the arrow pointed to. Two flanker arrows identical in shape and size to the target appeared 22 mm above and below the center of the target arrow 100 ms prior to each target arrow. Both flankers either pointed in the same (congruent) or opposite (incongruent) direction as the target. Hence, the greatest conflict monitoring was experienced during the incongruent condition. When the target appeared, both target and flankers remained on the screen for a further 150 ms, with a new trial being presented every 1650 ms. Trials were arranged in 10 blocks of 40 trials with 200 congruent and 200 incongruent trials. The task lasted 13 min. For further details on the task, see the Supplementary material. Mean reaction time (MRT), RTV (SD of reaction times), and number of errors (left-right errors occurring when participants chose the wrong left or right response) were calculated separately for congruent and incongruent conditions.

2.4. Electroencephalogram (EEG) recording and processing

The EEG was recorded from a 62-channel DC-coupled recording system (extended 10–20 montage) (Brain Products, Gilching, Germany), using a 500 Hz sampling-rate, impedances under 10 k Ω , and FCz as the recording reference. The electro-oculograms (EOGs) were recorded from electrodes above and below the left eye and at the outer canthi. Raw EEG recordings were pre-processed and analysed using Brain Vision Analyzer 2.0 (Brain Products, Gilching, Germany). The data were down-sampled to 256 Hz, re-referenced to the average of all electrodes (turning FCz into an active channel), and filtered using Butterworth band-pass filters (0.1–30 Hz, 24 dB/octave). Visual inspection was carried out to manually remove artefacts (e.g. from electrical noise or obvious movement). Independent component analysis (Jung et al., 2000) was used to correct ocular (blink-related and vertical and horizontal eye movements) artefacts. Sections of data containing artefacts exceeding $\pm 100 \mu\text{V}$ or with a

voltage step $>50 \mu\text{V}$ were automatically rejected. Baseline correction was performed using a -300 to -100 ms pre-target (-200 to 0 ms pre-flanker) interval. Researchers were blind to group status during EEG processing.

After averaging, the electrodes and latency windows for ERP analyses were selected based on previous studies with this task (Albrecht et al., 2008; Johnstone et al., 2009; McLoughlin et al., 2009; Michelini et al., 2016a), and verified against the topographic maps and grand averages in this sample (Fig. 1). The N2 was measured separately in stimulus-locked congruent and incongruent trials with correct responses, as maximum negative peak at Fz between 200 and 450 ms after target onset (Fig. 1). We further measured the N1 peak preceding the N2 as maximum negative peak between 100 and 200 ms at Fz, where this component was maximal (Fig. 1). Although N1 components have been previously examined both over frontal (Dong and Zhong, 2017; Johnstone et al., 2009; Vogel and Luck, 2000) and occipital sites (Butler et al., 2007; Vogel and Luck, 2000; Woltering et al., 2013), this frontal electrode was chosen for measuring the N1 here as the same scalp location was also used for the N2. This allowed us to examine whether group differences on the frontal N2 were partly accounted for by the earlier frontal N1 peak. ERN and Pe were measured in response-locked incongruent trials with incorrect responses (too few errors occurred in congruent trials, similar to previous studies Albrecht et al., 2008; McLoughlin et al., 2009; Michelini et al., 2016a). The ERN was measured at FCz between 0 and 150 ms as a difference from the amplitude of the preceding positivity (PNe, -100 to 50 ms) (Fig. S1), following a robust peak-to-peak approach (Falkenstein et al., 2000; Nieuwenhuis et al., 2001) that has proven sensitive to ADHD-control difference in previous studies using this task (Albrecht et al., 2008; McLoughlin et al., 2009; Michelini et al., 2016a). The Pe was measured as maximum positive peak at Cz between 150 and 450 ms after an incorrect response (Fig. S2).

2.5. Statistical analyses

All analyses were conducted in Stata 14 (StataCorp, 2015). MRT, RTV, number of errors, N1 and N2 from congruent and incongruent task conditions were analysed using random-intercept linear models (i.e., repeated-measure multilevel regressions), testing for main effects of group (ADHD, BD and controls), condition (congruent, incongruent), and group-by-condition interaction. Significant ($p < 0.05$) effects were followed up with post-hoc analyses testing for (i) between-group differences in congruent and incongruent conditions separately, and (ii) within-group differences across congruent and incongruent conditions. We further tested whether differences in the N1 amplitude contributed to differences in the subsequent N2 peak, in line with previous studies examining the overlap between ERP components (Cheung et al., 2017; Klawohn et al., 2020). An identical model, with N1 as a covariate, was thus run for the N2. The ERN and Pe, measured in incongruent trials only, were analysed with regression models with dummy variables to identify overall group effects, followed by post-hoc comparisons. Total errors, RTV and ERN showed skewed distributions and were transformed to normal with logarithm ("lnskew0" Stata command). For between-group comparisons, we report both p-values and Cohen's d effect sizes (with 95% confidence intervals), where $d \geq 0.20$ constitutes a small effect, $d \geq 0.50$ a medium effect and $d \geq 0.80$ a large effect (Cohen, 1988).

One participant with ADHD and one control were excluded from all ERP and cognitive-performance analyses because they failed to understand the task, as evident from incorrect responses in $>60\%$ trials and EEG recording notes. At least 20 clean segments were required for N1 and N2 analysis in line with previous literature (McLoughlin et al., 2009), thus one participant with ADHD was excluded. Due to a lower number of available clean segments for the ERN and Pe (given the low number of errors made by participants) and literature suggesting that fewer clean segments are sufficient to reliably measure these

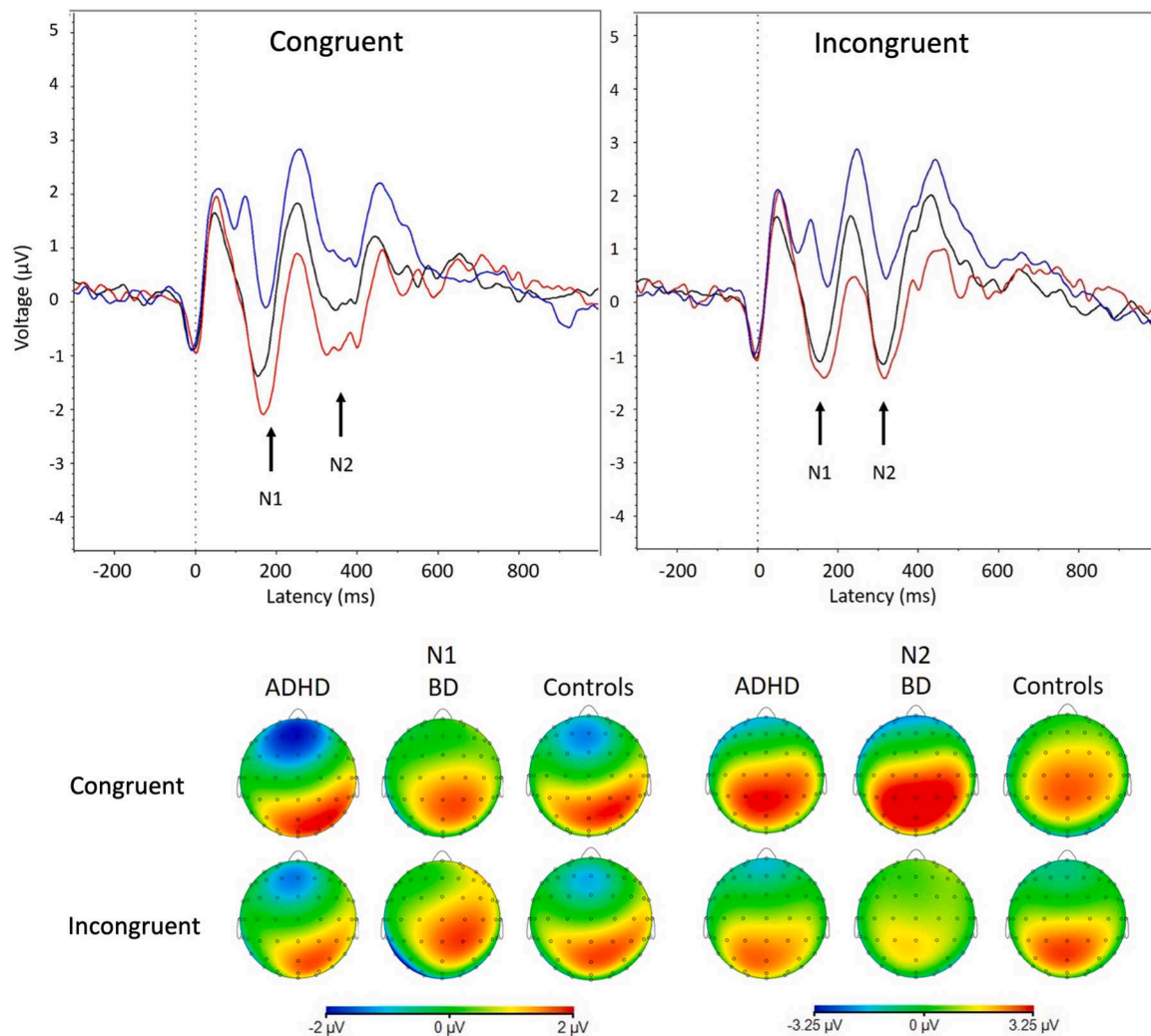


Fig. 1. Grand average stimulus-locked event-related potentials of the N1 and N2 at the Fz electrode after congruent (left) and incongruent (right) stimuli with correct responses for attention-deficit/hyperactivity disorder (ADHD, in red), bipolar disorder (BD, in blue) and control participants (in black), with topographical maps (top row = congruent, bottom row = incongruent). The N1 and N2 were measured at Fz between 100 and 200 ms and between 200 and 450 ms after target onset, respectively.

components (Foti et al., 2013; Hajcak et al., 2017; Rietdijk et al., 2014), participants with at least 15 clean segments were included for the ERN and Pe analyses. Accordingly, 3 participants with BD and 3 controls were removed from the ERN and Pe analysis. A sensitivity analysis on ERN and Pe on participants with at least 20 available segments was also carried out (Supplementary material).

3. Results

3.1. Cognitive performance

MRT ($F = 651.8$) and number of errors ($F = 264.5$) showed significant condition effects (both $p < 0.001$) but no group ($F = 0.79$, $p = 0.455$ and $F = 0.99$, $p = 0.373$) or group-by-condition interaction ($F = 0.01$, $p = 0.989$ and $F = 0.37$, $p = 0.693$) effects. Post-hoc analyses of condition effects within each group showed slower MRT and more errors in the incongruent than in the congruent condition in all groups (Table S2). No significant effects of group ($F = 1.29$, $p = 0.276$), condition ($F = 2.29$, $p = 0.130$) or group-condition interaction ($F = 1.82$, $p = 0.162$) emerged for RTV.

3.2. ERP components

Significant group ($F = 4.25$, $p = 0.014$) and condition ($F = 10.84$, $p = 0.001$) effects, but no group-by-condition interaction ($F = 0.63$, $p = 0.533$), emerged for the N2 (Fig. 1). Post-hoc tests demonstrated that in the congruent condition participants with BD had a significantly attenuated (less negative) N2 compared to participants with ADHD, while controls did not differ significantly from the other groups (Table 2). In the incongruent condition, the BD group showed a significantly reduced N2 relative to both the ADHD and control groups, which did not differ from one another. Post-hoc analyses of within-group condition effects showed that control participants had a significantly more negative N2 in the incongruent than in the congruent condition, participants with ADHD had a trend-level effect in the same direction (Table S2), while participants with BD did not show a significant N2 difference between conditions.

Significant group effects ($F = 4.19$, $p = 0.015$) but no effect of condition ($F = 2.18$, $p = 0.140$) or group-by-condition interaction ($F = 0.49$, $p = 0.614$) emerged for N1 (Fig. 1). Post-hoc group comparisons showed that participants with BD had a significantly lower N1 than participants with ADHD in both conditions. The N1 of participants with BD was also lower than that of controls in the congruent condition, with a trending

Table 2

Group comparison on cognitive and EEG measures in the congruent and incongruent conditions.

	Congruent ADHD vs BD		ADHD vs Control		BD vs Control		Incongruent ADHD vs BD		ADHD vs Control		BD vs Control	
	d [95% CI]	p	d [95% CI]	p	d [95% CI]	p	d [95% CI]	p	d [95% CI]	p	d [95% CI]	p
N1	1.00 [0.33, 1.66]	0.003**	0.30 [−0.35, 0.93]	0.317	0.65 [0.00, 1.29]	0.049*	0.75 [0.09, 1.41]	0.011*	0.17 [−0.47, 0.82]	0.426	0.51 [−0.13, 1.15]	0.081
N2	0.85 [0.19, 1.50]	0.014*	0.47 [−0.18, 1.11]	0.196	0.41 [−0.23, 1.04]	0.250	0.73 [0.07, 1.38]	0.003**	0.24 [−0.41, 0.88]	0.336	0.60 [−0.04, 1.24]	0.049*

Data on cognitive performance measures were analysed with 19 ADHD, 20 BD and 19 controls; data for the N1 and N2 congruent trials were analysed with 19 ADHD, 20 BD and 19 controls; data for the N1 and N2 incongruent trials were analysed with 18 ADHD, 20 BD and 19 controls. 95% CI 95% confidence intervals around *d* estimates, *ADHD* attention-deficit/hyperactivity disorder, *BD* bipolar disorder, *d* Cohen's *d*, *N1* N1 ERP, *N2* N2 ERP, *p* value from mixed model post hoc tests.

***p* < 0.01, **p* < 0.05. Bold=large effect size (*d* ≥ 0.80); Italics=medium effect size (*d* ≥ 0.50).

non-significant difference in the incongruent condition (Table 2). Participants with ADHD did not differ from controls on the N1 in either condition (Table 2).

With N1 as a covariate, a significant condition effect ($F = 12.26$, $p < 0.001$), but no group ($F = 1.57$, $p = 0.208$) or group-by-condition interaction ($F = 0.77$, $p = 0.463$) effects, emerged on the N2. The N1 was significantly associated with N2 ($p < 0.001$). This result suggests that, once controlling for earlier group differences in the N1, the group effect on the N2 was no longer significant. The pattern of post-hoc analyses of condition effects were unchanged, though the difference between conditions in participants with ADHD was significant rather than at trend level (Table S2).

No significant group effect emerged for ERN ($p = 0.447$) or Pe ($p = 0.128$) (Fig. S2). Results were unchanged in participants with at least 20 clean segments (see Supplementary materials).

4. Discussion

In this ERP study we have conducted the first direct comparison between women with ADHD and women with BD during a performance-monitoring task. We observed, in line with our hypothesis, a reduced N2, reflecting impaired conflict monitoring, in individuals with BD compared to individuals with ADHD and controls. However, this N2 difference was no longer evident when accounting for an earlier difference in N1 amplitude, reflecting early-attentional processes (Dong and Zhong, 2017; Johnstone et al., 2009) in individuals with BD compared to those with ADHD and controls. Differential activity between participants with ADHD and BD in conflict monitoring during this task was thus likely reflecting a preceding impairment in early stimulus processing specific to BD. These findings showing BD-specific N1 reductions indicate differences in early attentional processes between BD and ADHD, which, if replicated, may potentially point to distinct neural mechanisms implicated in the two disorders.

A reduced N2 amplitude, specific to women with BD, distinguished them from women with ADHD during both congruent and incongruent conditions, as well as from control women in the incongruent condition. In high-conflict tasks such as the version of the flanker task used here, an N2 reduction arises from a reduced ability to process two parallel and conflicting stimuli (Folstein and Van Petten, 2008). This result is consistent with the BD-specific impairment in N2 that we found in this sample during the CPT-OX task, which evokes lower conflict-monitoring demands (Micheline et al., 2016b). However, our additional analysis – the first direct comparison between ADHD and BD groups on the N1 – suggested that the distinctive ERP activity of the BD group more likely originated from the preceding N1 peak. Specifically, the N1 was reduced in the BD group compared to the other groups, accounting for the N2 group difference. A clear N1 did not emerge in our study on the CPT-OX (Micheline et al., 2016b), suggesting that our previous N2 finding was likely not confounded by this early peak. These findings indicate the importance of examining earlier phases of stimulus processing on downstream brain activity related to cognitive processes, such as conflict monitoring, thus leveraging the excellent temporal resolution of

EEG. Across groups, unlike the N2, the N1 was comparable across congruent and incongruent trials, suggesting that it was not modulated by conflict. This is consistent with the interpretation of the N1 as a low-level, early-attentional component related to capacity allocation or preparatory processes (Dong and Zhong, 2017; Johnstone et al., 2009; Näätänen and Michie, 1979; Vogel and Luck, 2000).

The current study further extends the limited existing research on ERP components in individuals with euthymic BD. Beside elucidating the presence of N2 impairments, our N1 finding is consistent with a few previous studies which found atypical amplitudes of early (<200 ms post-stimulus) ERP components in individuals with BD (Cabranes et al., 2013; Jahshan et al., 2012; Yeap et al., 2009), although not with one study reporting intact N1 during a flanker task (Morsel et al., 2014). Future studies should test whether early-attentional N1 impairments are associated with the attentional problems experienced by individuals with BD, such as distractibility during mania and difficulties concentrating during depression. The further examination of ERN and Pe components extends the literature on error processing among individuals with BD. The lack of differences between women with BD and control women is consistent with previous evidence of intact ERN (Kopf et al., 2015) and Pe (Minzenberg et al., 2014; Morsel et al., 2014) in individuals with BD, but not with other data indicating reductions in these peaks (Kopf et al., 2015; Morsel et al., 2014). Our findings showing intact ERN, but reduced N1 and N2, among individuals with BD suggest a partial functional dissociation between error processing and stimulus processing during high-conflict trials, in line with recent studies (Cohen and van Gaal, 2014; Iannaccone et al., 2015; Michelini et al., 2016a). These findings challenge prior accounts positing that ERN and N2 reflect a common performance monitoring mechanism (Yeung and Cohen, 2006), as well as studies suggesting similarities between the ERN and N1 components (Carmi et al., 2019; Jelinić et al., 2020; Suzuki and Shinoda, 2011). Future studies further investigating N1, N2 and ERN components are needed to clarify whether these ERPs reflect similar or distinct underlying mechanisms and whether individuals with euthymic BD show impairments in specific ERPs during performance monitoring tasks, but not others.

The ADHD group did not differ from controls in the N1, in line with most previous studies, including one using a flanker task (Johnstone et al., 2009), which examined this component in individuals with ADHD (Fisher et al., 2011; Johnstone et al., 2009; Woltering et al., 2013). In contrast, we did not find reductions in N2, ERN or Pe in the ADHD group in comparison to the control group during this flanker task. Participants with ADHD also showed comparable task performance to controls. The lack of differences from the control group in ERP and performance measures may be attributable to sex effects, as ours is the first study focused on an all-female sample, while most previous studies reporting impairments in ERPs and performance used all- or predominantly-male samples (Albrecht et al., 2008; Groom et al., 2010; McLoughlin et al., 2009; Michelini et al., 2016a). The current sample of women was also on average older than previous male samples that found differences between ADHD and control groups using this task (McLoughlin et al., 2009; Michelini et al., 2016a). As previous evidence suggests that group

differences might be larger in younger adults than in older adults (Herrmann et al., 2010), this age difference may be a possible explanation for the similarity between ADHD and control groups in this sample. A lack of differences in IQ between the ADHD and control groups in this sample may have further contributed to the non-significant differences, as in our previous larger and more heterogeneous study we found that ADHD-control differences during this task were reduced or null when controlling for IQ (Michellini et al., 2019, 2016a). Future larger-scale studies, including both males and females with a wider range of IQs and ages, are needed to examine potential differences in cognitive and ERP indices of performance-monitoring processes in men and women with ADHD.

Three main limitations should be considered when interpreting these results. Firstly, despite the groups being matched on sex, age and IQ, there was a discrepancy in the presence of prescribed medication across the groups. Though participants with ADHD stopped taking stimulant medication 48 h prior to assessments, for ethical reasons the same was not asked of participants on mood-stabilizing, anti-psychotic or antidepressant treatments. Small numbers in each medication subgroup did not allow us to investigate the effect of medication. However, previous studies suggest that medication may show positive effects (e.g., reducing differences between individuals with BD and controls) or no effects on cognitive-EEG measures (Degabriele and Lagopoulos, 2009; Galletly et al., 2005; Morsel et al., 2018). As such, while the possibility remains that the lack of group differences on the ERN and Pe may have been influenced by medication effects, it might be unlikely that the significant N1 and N2 reductions in participants with BD reflect confounding medication effects. Future work should examine unmedicated participants or directly investigate medication differences in large samples. Secondly, even though we were able to detect medium-to-large group effects as statistically significant in the N1 and N2, the sample was relatively small, and some participants had to be excluded from the ERN/Pe analysis due to limited number of errors. Although the current study represents the first to date to carefully compare individuals with ADHD, with BD and without either disorder on performance-monitoring measures, future larger-scale studies are needed to confirm these findings and to potentially reveal subtler group differences. Thirdly, the current study included individuals with ADHD or BD-I diagnoses, but excluded individuals with comorbid presentations or other types of BD (e.g., BD-II and cyclothymic disorder). Since comorbidity between ADHD and BD is common in clinical settings, and other types of BD also share clinical features with ADHD (Skirrow et al., 2012), future research is needed to examine the same ERPs also in individuals with these clinical presentations. Such research would provide further insights into the shared mechanisms between ADHD and BD and may potentially point to specific features of comorbid and “pure” presentations.

In conclusion, our results show a disorder-specific attenuation of an early-attentional N1 component in women with BD compared with women with ADHD during a performance-monitoring task. This early differential activity may contribute to a downstream difference that we observed between these groups in the conflict-monitoring N2, and highlights the importance of considering possible influences in preceding stages of stimulus processing when interpreting ERP impairments in psychiatric disorders. If replicated in future larger-scale studies, the early attentional impairments characterizing women with BD may be employed for developing biomarkers for monitoring treatment effects on attentional dysfunction among individuals with BD.

Contributors

Prof Jonna Kuntsi and Dr Viryanaga Kitsune were involved in funding acquisition. Prof Jonna Kuntsi, Prof Philip Asherson, Dr Viryanaga Kitsune and Dr Georgina Hosang were involved in conceptualisation of the study. Dr Viryanaga Kitsune and Dr Giorgia Michellini conducted the investigation. Formal analysis was conducted by Sophie Carruthers and Dr Giorgia Michellini. Study supervision was

provided by Prof Jonna Kuntsi, Prof Philip Asherson, and Prof Daniel Brandeis. The original draft of the manuscript was conducted by Sophie Carruthers, Dr Giorgia Michellini and Prof Jonna Kuntsi. All authors contributed to reviewing and editing of the manuscript.

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Declaration of Competing Interest

Prof Jonna Kuntsi has given talks at educational events sponsored by Medice; all funds are received by King's College London and used for studies of ADHD. Prof Philip Asherson has received funding for research by Vifor Pharma and has given sponsored talks and been an advisor for Shire, Janssen-Cilag, Eli-Lilly, Flynn Pharma and Pfizer, regarding the diagnosis and treatment of ADHD. All funds are received by King's College London and used for studies of ADHD. The other authors report no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.psychres.2021.114088](https://doi.org/10.1016/j.psychres.2021.114088).

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